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(54) **Salts of 5'-methylthio-5'-deoxyadenosine with long-alkyl chain sulphonic acids.**

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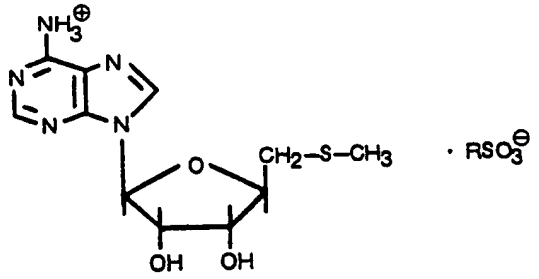
Description

This invention relates to new salts of 5'-methylthio-5'-deoxyadenosine (MTA) with long-alkyl chain sulphonic acids, and having the following general formula



(I)

in which R is a linear or branched alkyl radical containing 6—18 carbon atoms.

The invention also relates to the process for producing said salts and to the pharmaceutical forms containing said salts as active principle.

Their possible therapeutic applications make these salts of considerable interest.

They possess central and peripheral vasodilatory activity, platelet antiaggregation activity, antiinflammatory, analgesic and antipyretic activity, and can find clinical application in the treatment of cerebral and peripheral vasculopathies of the presenile and senile age, in which the atherosclerotic degenerative process in the vasal wall alters the hematic flow, with negative consequences for the microcirculation.

In this context, the antiaggregation activity also plays an important role in that it prevents extension of intimal degenerative lesions.

The MTA salts according to the present invention can be presented either in injectable forms or in oral formulations as tablets, pills, capsules, sustained-release capsules, sustained-release tablets, gastroresistant tablets, sachets, syrups, extemporaneous syrups, sustained-release syrups and other forms normally used in pharmaceutics.

Other pharmaceutical forms can also be provided such as suppositories, creams, ointments and unguents.

The process for producing the MTA salts according to the present invention is characterised by dissolving the sodium salt of the chosen sulphonic acid in distilled water, dissolving the MTA in distilled water to which concentrated H_2SO_4 has been added, reacting together the two solutions to precipitate the MTA sulphonate, and recovering said salt with a high degree of purity.

These and other characteristics of the process according to the present invention, and of the products obtained and the relative pharmaceutical formulations, will be more apparent from the detailed description given hereinafter together with the examples, which are described for non-limiting illustrative purposes only.

The MTA salts according to the present invention can be easily prepared by operating in accordance with the following stages:

preparation of MTA;

preparation of the sodium salt of the chosen sulphonic acid;

precipitation of the MTA salt by bringing the solutions of the products of the two preceding stages into contact;

filtering off and drying the MTA salt.

The MTA is preferably prepared by the process of the present applicant (USA patent 4,454,122) by which bread yeast cells enriched in S-adenosylmethionine is lysed by treatment with ethyl or methyl acetate, the solution is concentrated under vacuum at 35—40°C, the S-adenosylmethionine is hydrolysed by boiling under reflux, the pH is adjusted to 7 and finally the solution is cooled to 0—5°C and the precipitated MTA recovered.

The sulphonic acid sodium salts are preferably prepared by the process described in Italian patent application 20940 A/84 (EP—A—162 324) of the present applicant, by which the relative bromoalkanes to which water and alcohol have been added are treated with sodium sulphite while boiling under reflux. On termination of the reaction, which proceeds in accordance with the chemical equation $RBr+Na_2SO_3 \rightarrow RSO_3Na+NaBr$, the product mixture is diluted with distilled water, heated until complete dissolution, and crystallised at 15°C. The product is filtered off, washed with water and then with acetone, suspended in acetone and heated in order to extract the fatty alcohol by-product. The product is cooled, filtered, washed with acetone and dried under vacuum.

The MTA salt is prepared by the following process:

the sodium salt of the chosen sulphonic acid is dissolved in the minimum quantity of distilled water, possibly heating to a temperature of 35—60°C to favour dissolution, the precise water quantities used per

mole of sulphonate being as follows: 3 litres for hexanesulphonate, 10 litres for octanesulphonate, 15 litres for decanesulphonate, 20 litres for dodecanesulphonate, 30 litres for tetradecanesulphonate, 40 litres for hexadecanesulphate and 50 litres for octadecanesulphonate;

the MTA is dissolved in distilled water containing sulphuric acid, possibly heating to a temperature of 40-60°C, the distilled water being in the region of 3 litres per mole of MTA andthe sulphuric acid being in the region of 0.5 moles per mole of MTA;

the MTA solution cooled to 15—25°C is added under agitation to the sulphonic acid sodium salt solution at a temperature of between 35 and 60°C, the two reagents being in equimolar quantities, the mixture being kept under agitation and cooled to a temperature of 15—25°C for a time of between 0.5 and 20 hours, and preferably for a time of between 3 and 4 hours, in order to transform the obtained MTA salt from amorphous to microcrystalline;

the MTA salt is separated preferably by pressure filtration or centrifuging, it is washed carefully with distilled water and dried under vacuum, using a residual pressure of less than 1 mmHg, at a temperature of 40°C.

The yield varies from 80% to 95% according to the type of salt; the purity of the obtained salt exceeds 99%.

Example 1

Preparation of MTA hexanesulphonate

18.85 kg (100 moles) of sodium hexanesulphonate are dissolved in 300 litres of distilled water at 40°C.

29.7 kg (100 moles) of MTA are dissolved in a further separate 300 litres of distilled water containing 4.9 kg (50 moles) of concentrated sulphuric acid. The mixture is heated to 50°C to favour dissolution, and then cooled to 20°C.

This latter solution is added under agitation to the sodium hexanesulphonate solution, and the mixture cooled to 20°C.

It is left under agitation for 3 hours. A crystalline precipitate is obtained, which is filtered off in a filter press and washed with 50 litres of distilled water. The mother liquors are collected and concentrated to a volume of 100 litres.

This concentrate is cooled to 20°C and left under agitation for 3 hours.

A white microcrystalline precipitate is obtained, which is filtered off in a pressure filter and washed with 10 litres of distilled water.

The two precipitates obtained in this manner are placed in a dryer under vacuum at 40°C and 0.5 mmHg of residual pressure until the residual product moisture content is 2%.

37 kg of white powder are obtained, which on analysis shows the following composition:

MTA	63%
Hexanesulphonic acid	35%
H_2O	2%

Yield = 79.9%.

The product is in the form of a white powder which is relatively poorly soluble in water but soluble in methanol and ethanol.

On HPLC analysis (column PARTISIL® 10 SCX, eluent 0.2 M ammonium formate, pH=4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to that of the basic MTA.

Elementary analysis: $C_{11}H_{15}N_5O_3S \cdot C_6H_{14}O_3S$

	N	C	H
Calculated %	15.1	44.05	6.3
Found %	15.1	44.1	6.4

The product ultraviolet spectrum (3 mg in 100 ml 1N H_2SO_4) shows an absorption maximum at 257 nm with $E_{1\%}$=321.

Example 2

Preparation of MTA octanesulphonate

21.65 kg of sodium octanesulphonate (100 moles) are dissolved in 1000 litres of distilled water at 40°C.

The procedure of Example 1 is followed until the product is completely dry. 40 kg of white powder are obtained which on analysis shows the following composition:

MTA	59.3%
Octanesulphonic acid	38.7%
H_2O	2%

Yield = 81.4%

The product is in the form of a white powder which is relatively poorly soluble in water but soluble in methanol and ethanol.

On HPLC analysis (column PARTISIL 10SCX, eluent 0.2 M ammonium sulphate, pH=4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to the basic MTA.

Elementary analysis: $C_{11}H_{15}N_5O_3S \cdot C_8H_{18}O_3S$

	N	C	H
Calculated %	14.25	46.4	6.8
Found %	14.3	46.5	6.8

The product ultraviolet spectrum (3 mg in 100 ml 1N H_2SO_4) shows an absorption maximum at 257 mn with $E_{1\%}$=302.

Example 3

Preparation of MTA decanesulphonate

24.45 kg of sodium decanesulphonate (100 moles) are dissolved in 1500 litres of distilled water at 40°C.

The procedure of Example 1 is followed until the product is completely dry. 44.5 kg of white powder are obtained, which on analysis shows the following composition:

MTA	56.1%
Decanesulphonic acid	41.9%
H_2O	2%

Yield = 85.6%

The product is in the form of a white powder which is poorly soluble in water but soluble in methanol and ethanol.

On HPLC analysis (column PARTISIL 10SCX, eluent 0.2M ammonium formate, pH = 4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to that of the basic MTA.

Elementary analysis: $C_{11}H_{15}N_5O_3S.C_{10}H_{22}O_3S$

	N	C	H
Calculated %	13.5	48.5	7.2
Found %	13.5	48.5	7.1

The product ultraviolet spectrum (3 mg in 100 ml 1N H_2SO_4) shows a maximum absorption at 257 mm with $E_{1\%}$ = 286.

Example 4

Preparation of MTA dodecanesulphonate

27.25 kg of sodium dodecanesulphonate (100 moles) are dissolved in 2000 litres of distilled water at 40°C.

29.7 kg (100 moles) of MTA are dissolved separately in 300 litres of distilled water containing 4.9 kg (50 moles) of concentrated sulphuric acid.

The mixture is heated to 50°C to favour dissolution, and is then cooled to 20°C.

This latter solution is poured under agitation into the sodium dodecanesulphonate solution, and the mixture cooled to 20°C.

It is left under agitation for 3 hours.

A microcrystalline white precipitate is obtained, which is filtered off in a pressure filter and washed with 100 litres of distilled water.

The precipitate thus obtained is placed in a vacuum dryer at 40°C and 0.5 mmHg of residual pressure

until the residual product moisture content is 2%.

49.2 kg of white powder are obtained, which on analysis shows the following composition:

MTA	53.2%
Dodecanesulphonic acid	44.8%
H_2O	2%

Yield = 89.9%

The product is in the form of a white powder which is insoluble in water but soluble in methanol, ethanol and 2:1 methanol-chloroform mixtures. On HPLC analysis (column PARTISTIL 10 SCX, eluent 0.2M ammonium formate, pH = 4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to that of the basic MTA.

Elementary analysis: $C_{11}H_{16}N_6O_3S.C_{12}H_{26}O_3S$

	N	C	H
Calculated %	12.8	50.4	7.6
Found %	12.8	50.3	7.7

The product ultraviolet spectrum (3 mg in 100 ml of 1N H_2SO_4) shows an absorption maximum at 257 mn with $E_{1\%} = 271$.

Example 5

Preparationof MTA tetradecanesulphonate

30.05 kg of sodium tetradecanesulphone (100 moles) are dissolved in 3000 litres of distilled water at 50°C.

The procedure of Example 4 is followed until the product is completely dry. 52.9 kg of white powder are obtained, which on analysis shows the following composition:

MTA	50.6%
Tetradecanesulphonic acid	47.4%
H_2O	2%

Yield = 91.9%

The product is in the form of a white powder which is insoluble in water but soluble in methanol, ethanol and 2:1 methanol-chloroform mixtures.

On HPLC analysis (column PARTISIL 10 SCX, euent, 0.2M ammonium formate, pH = 4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to that of the basic MTA.

Elementary analysis: $C_{11}H_{16}N_5O_3S.C_{14}H_{30}O_3S$

	N	C	H
Calculated %	12.2	52.1	7.9
Found %	12.1	52.1	7.9

The product ultraviolet spectrum (3 mg in 100 ml 1N H_2SO_4) shows an absorption maximum at 257 mn with $E_{1\%} = 258$.

Example 6

Preparation of MTA hexadecanesulfphonate

32.85 kg of sodium hexadecanesulphonate (100 moles) are dissolved in 4000 litres of distilled water at 60°C.

The procedure of Example 4 is followed until the product is completely dry.

56.7 kg of white powder are obtained, which on analysis shows the following composition:

MTA	48.2%
Hexadecanesulphonic acid	49.8%
H_2O	2%

Yield = 94%

The product is in the form of a white powder which is insoluble in water but soluble in methanol, ethanol and 2:1 methanol-chloroform mixtures.

On HPLC analysis (column PARTISIL 10 SCX, eluent 0.2M ammonium formate, pH = 4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to that of the basic MTA.

Elementary analysis: $C_{11}H_{15}N_5O_3S.C_{16}H_{34}O_3S$

	N	C	H
Calculated %	11.6	53.7	8.2
Found %	11.6	53.6	8.2

The product ultraviolet spectrum (3 mg in 100 ml 1N H_2SO_4) shows an absorption maximum at 257 mn with $E_{1\%} = 246$.

Example 7

Preparation of MTA octadecanesulphonate

35.65 kg of sodium octadecanesulphonate (100 moles) are dissolved in 5000 litres of distilled water at 60°C.

The procedure of Example 4 is followed until the product is completely dry.

60 kg of white powder are obtained, which on analysis shows the following composition:

MTA	46.1%
Octadecanesulphonic acid	51.9%
H_2O	2%

Yield = 95%

The product is in the form of a white powder which is insoluble in water, slightly soluble in methanol and ethanol, and soluble in 2:1 methanol-chloroform mixtures.

On HPLC analysis (column PARTISTIL 10 SCX, eluent 0.2M ammonium formate, pH = 4, throughput 1 ml/min) the product shows a single peak with a retention time of 350 seconds, exactly corresponding to that of the basic MTA.

Elementary analysis: $C_{11}H_{15}N_5O_3S.C_{18}H_{38}O_3S$

	N	C	H
Calculated %	11.1	55.1	8.5
Found %	11.2	55.2	8.5

The product ultraviolet spectrum (3 mg in 100 ml 1N H_2SO_4) shows an absorption maximum at 257 nm with $E_{1\%} = 235$.

Example 8

Preparation of gastrosoluble tablets

a) A 200 mg tablet contains:

MTA octadecanesulphonate	434 mg
equivalent to a basic MTA quantity of	200 mg
Cross-linked carboxymethylcellulose	50 mg
Magnesium stearate	10 mg
Microcrystalline cellulose to make up to	600 mg

b) A 200 mg tablet contains:

MTA dodecanesulphonate	376 mg
equivalent to a basic MTA quantity of	200 mg
Corn starch	80 mg
Polyvinylpyrrolidone	20 mg
Magnesium stearate	10 mg

c) A 200 mg tablet contains:

MTA hexadecanesulphonate	415 mg
equivalent to a basic MTA quantity of	200 mg
Sodium chloride	100 mg
Polyvinylpyrrolidone	20 mg
Corn starch to make up to	650 mg

Example 9

Preparation of injectable solutions

A lyophilised vial contains:

MTA hexanesulphonate	79.4 mg
equivalent to a basic MTA quantity of	50 mg
Mannitol	100 mg

A solvent vial contains:

Citrated buffer to make up to	pH 5
Bidistilled water to make up to	5 ml

Example 10

Preparation of an extemporaneous solution for oral use

A bottle contains:

MTA hexanesulphonate	159 mg
equivalent to a basic MTA quantity of	100 mg
Saccharose	100 mg
Flavourings and preservatives	
Bidistilled water to make up to	10 ml

Example 11

Preparation of chronoids

A 100 mg capsule contains:

MTA octadecanesulphonate	217 mg
equivalent to a basic MTA quantity of	100 mg
Sugar chronoids	200 mg

Example 12

Preparation of capsules

A 100 mg capsule contains:

MTA hexadecanesulphonate	207.5 mg
equivalent to a basic MTA quantity of	100 mg
Mannitol	50 mg
Lactose	50 mg
Magnesium stearate	12 mg

Example 13

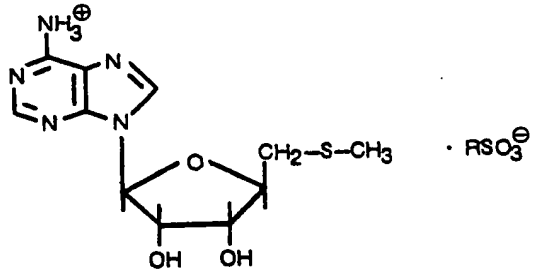
Preparation of suppositories

A 200 mg suppository contains:

MTA octadecanesulphonate	434 mg
equivalent to a basic MTA quantity of	200 mg
Suppository mass to make up to	2500 mg

Claims for the Contracting States: BE CH DE FR GB LI LU NL SE

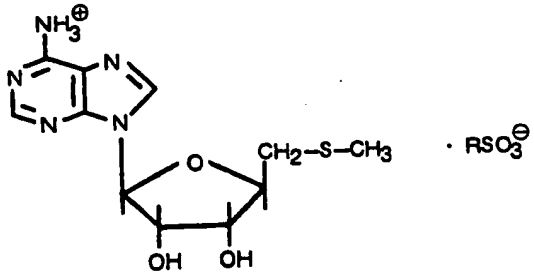
1. Salts of 5'-methylthio-5'-deoxyadenosine (MTA) with long-alkyl chain sulphonic acids, characterised by the following general formula:



(I)

in which R is a linear or branched alkyl radical containing 6—18 carbon atoms.

2. A process for preparing salts of 5'-methylthio-5'-deoxyadenosine (MTA) with long-alkyl chain sulphonic acids, and having the following general formula:



(I)

in which R is a linear or branched alkyl radical containing 6—18 carbon atoms, characterised by dissolving the sodium salt of the chosen sulphonic acid in distilled water, dissolving the MTA in distilled water to which concentrated H_2SO_4 has been added, reacting together the two solutions to precipitate the MTA sulphonate, and recovering this latter salt with a high degree of purity.

3. A process as claimed in claim 2, characterised in that the sulphonic acid sodium salt undergoes said dissolving at a temperature of between 35 and 60°C, using the following water quantities per mole of salt: 3 litres for hexasulphonate, 10 litres for octanesulphonate, 15 litres for decanesulphonate, 20 liters for dodecanesulphonate, 30 litres for tetradecanesulphonate, 40 litres for hexadecanesulphonate and 50 litres for octadecanesulphonate.

4. A process as claimed in claim 2, characterised in that the MTA undergoes said dissolving at a temperature of between 40 and 60°C in a mixture of distilled water and H_2SO_4 containing 3 litres of distilled water and 0.5 moles of H_2SO_4 per mole of MTA.

5. A process as claimed in claim 2, characterised in that said reaction is effected by adding the MTA solution cooled to 15—25°C to the sulphonic acid sodium salt solution at a temperature of between 35 and 60°C under agitation, the two reagents being in equimolar quantities, the mixture being kept under agitation and cooled to a temperature of 15—25°C for a time of between 0.5 and 20 hours.

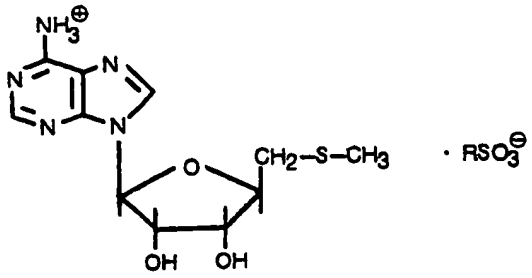
6. A process as claimed in claim 2, characterised in that the MTA sulphonate undergoes said recovery by filtration under pressure or by centrifuging followed by washing with distilled water and drying under vacuum at a temperature of 40°C.

7. Pharmaceutical compositions of central and peripheral vasodilatory, platelet antiaggregation, antiinflammatory, analgesic and antipyretic activity, comprising at least one compounds of general formula (I) as their active principle.

8. The use of a compound of general formula (I) for preparing pharmaceutical products of central and peripheral vasodilatory, platelet antiaggregation, antiinflammatory, analgesic and antipyretic activity.

Claims for the Contracting State: AT

1. A process for preparing salts of 5'-methylthio-5'-deoxyadenosine (MTA) with long-alkyl chain sulphonic acids, and having the following general formula:



(I)

in which R is a linear or branched alkyl radical containing 6—18 carbon atoms, characterised by dissolving the sodium salt of the chosen sulphonic acid in distilled water, dissolving the MTA in distilled water to which concentrated H_2SO_4 has been added, reacting together the two solutions to precipitate the MTA sulphonate, and recovering this latter salt with a high degree of purity.

2. A process as claimed in claim 2, characterised in that the sulphonic acid sodium salt undergoes said dissolving at a temperature of between 35 and 60°C, using the following water quantities per mole of salt: 3 litres for hexasulphonate, 10 litres for octanesulphonate, 15 litres for decanesulphonate, 20 liters for dodecanesulphonate, 30 litres for tetradecanesulphonate, 40 litres for hexadecanesulphonate and 50 litres for octadecanesulphonate.

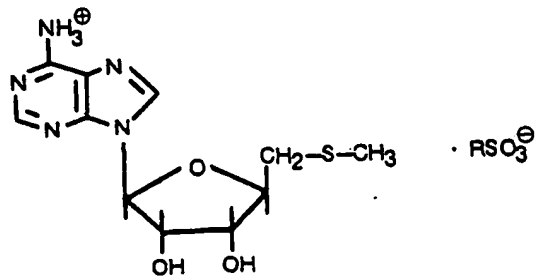
3. A process as claimed in claim 2, characterised in that the MTA undergoes said dissolving at a temperature of between 40 and 60°C in a mixture of distilled water and H_2SO_4 containing 3 litres of distilled water and 0.5 moles of H_2SO_4 per mole of MTA.

4. A process as claimed in claim 2, characterised in that said reaction is effected by adding the MTA solution cooled to 15—25°C to the sulphonic acid sodium salt solution at a temperature of between 35 and 60°C under agitation, the two reagents being in equimolar quantities, the mixture being kept under agitation and cooled to a temperature of 15—25°C for a time of between 0.5 and 20 hours.

5. A process as claimed in claim 2, characterised in that the MTA sulphonate undergoes said recovery by filtration under pressure or by centrifuging followed by washing with distilled water and drying under vacuum at a temperature of 40°C.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB LI LU NL SE

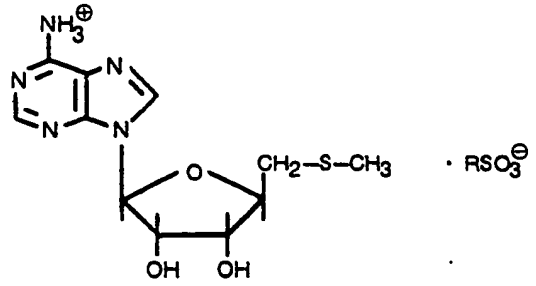
1. Salze von 5'-Methylthio-5'-desoxyadenosin (MTA) mit Sulfonsäure mit langer Alkylkette gekennzeichnet durch die folgende allgemeine Formel



(I)

worin R ein linearer oder verzweigter Alkylrest mit 6 bis 18 Kohlenstoffatomen ist.

2. Verfahren zum Herstellen von Salzen von 5'-Methylthio-5'-desoxyadenosin (MTA) mit Sulfonsäuren mit langer Alkylkette der folgenden allgemeinen Formel



(I)

worin R ein linearer oder verzweigter Alkylrest mit 6 bis 18 Kohlenstoffatomen ist, gekennzeichnet durch Lösen des Natriumsalzes der gewählten Sulfonsäure in destilliertem Wasser, Lösen des MTA in destilliertem Wasser, dem konzentrierte H_2SO_4 zugesetzt wurde, Umsetzen der beiden Lösungen zum Ausfällen des MTA-Sulfonats und Gewinnen dieses letzteren Salzes mit einem hohen Reinheitsgrad.

3. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß das Sulfonsäurenatriumsalz bei einer Temperatur von 35 bis 60°C unter Verwendung der folgenden Wassermengen pro Mol Salz gelöst wird: 3 l für Hexansulfonat, 10 l für Octansulfonat, 15 l für Decansulfonat, 20 l für Dodecansulfonat, 30 l für Tetradecansulfonat, 40 l für Hexadecansulfonat und 50 l für Octadecansulfonat.

4. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß das MTA bei einer Temperatur von 40 bis 60°C in einer Mischung von destilliertem Wasser und H_2SO_4 enthaltend 3 l destilliertes Wasser und 0,5 Mol H_2SO_4 pro Mol MTA gelöst wird.

5. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß diese Reaktion durch Zusetzen der auf 15 bis 25°C gekühlten MTA-Lösung zu der Sulfonsäurenatriumsalzlösung bei einer Temperatur von 35 bis 60°C unter Rühren bewirkt wird, wobei die beiden Reagentien in äquimolaren Mengen vorhanden sind, und die Mischung während einer Zeit von ½ bis 20 h gerührt und auf eine Temperatur von 15 bis 25°C gekühlt wird.

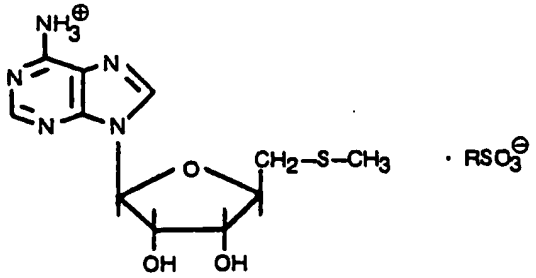
6. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß das MTA-Sulfonat durch Filtrieren unter Druck oder Zentrifugieren, gefolgt von Waschen mit destilliertem Wasser und Trocknen unter Vakuum bei einer Temperatur von 40°C gewonnen wird.

7. Pharmazeutische Zusammensetzungen mit zentraler und peripherer vasodilatatorischer, Blutplättchenantiaggregations-, entzündungschemmender, analgetischer und antipyretischer Wirksamkeit, umfassend mindestens eine Verbindung der allgemeinen Formel (I) als ihren Wirkstoff.

8. Verwendung einer Verbindung der allgemeinen Formel (I) zum Herstellen von pharmazeutischen Produkten mit zentraler und peripherer vasodilatatorischer, Blutplättchenantiaggregations-, entzündungshemmender, analgetischer und antipyretischer Wirksamkeit.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zum Herstellen von Salzen von 5'-Methylthio-5'-desoxyadenosin (MTA) mit Sulfonsäuren mit langer Alkylkette der folgenden allgemeinen Formel



(I)

worin R ein linearer oder verzweigter Alkylrest mit 6 bis 18 Kohlenstoffatomen ist, gekennzeichnet durch Lösen des Natriumsalzes der gewählten Sulfonsäure in destilliertem Wasser, Lösen des MTA in destilliertem Wasser, dem konzentrierte H_2SO_4 zugesetzt wurde, Umsetzen der beiden Lösungen zum Ausfällen des MTA-Sulfonats und Gewinnen dieses letzteren Salzes mit einem hohen Reinheitsgrad.

2. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß das Sulfonsäurenatriumsalz bei einer Temperatur von 35 bis 60°C unter Verwendung der folgenden Wassermengen pro Mol Salz gelöst wird: 3 l für Hexansulfonat, 10 l für Octansulfonat, 15 l für Decansulfonat, 20 l für Dodecansulfonat, 30 l für Tetradecansulfonat, 40 l für Hexadecansulfonat und 50 l für Octadecansulfonat.

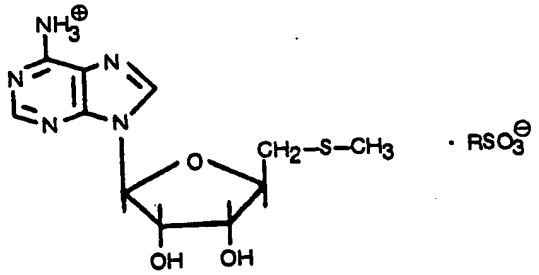
3. Verfahren, wie in Anspruch 1 beansprucht, dadurch gekennzeichnet, daß das MTA bei einer Temperatur von 40 bis 60°C in einer Mischung von destilliertem Wasser und H_2SO_4 enthaltend 3 l destilliertes Wasser und 0,5 Mol H_2SO_4 pro Mol MTA gelöst wird.

4. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß diese Reaktion durch Zusetzen der auf 15 bis 25°C gekühlten MTA-Lösung zu der Sulfonsäurenatriumsalzlösung bei einer Temperatur von 35 bis 60°C unter Rühren bewirkt wird, wobei die beiden Reagentien in äquimolaren Mengen vorhanden sind, und die Mischung während einer Zeit von ½ bis 20 h gerührt und auf eine Temperatur von 15 bis 25°C gekühlt wird.

5. Verfahren, wie in Anspruch 2 beansprucht, dadurch gekennzeichnet, daß das MTA-Sulfonat durch Filtrieren unter Druck oder Zentrifugieren, gefolgt von Waschen mit destilliertem Wasser und Trocknen unter Vakuum bei einer Temperatur von 40°C gewonnen wird.

Revendications pour les Etats contractants: BE CH DE FR GB LI LU NL SE

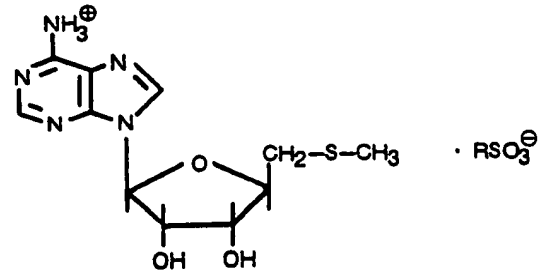
1. Sels de la 5'-méthylthio-5'-désoxyadénosine (MTA) avec des acides sulfoniques à chaîne alkyle de grande longueur, caractérisés par la formule générale suivante:



(I)

dans laquelle R est un radical alkyle linéaire ou ramifié en C_6 à C_{18}.

2. Procédé de préparation de sels de la 5'-méthylthio-5'-désoxyadénosine (MTA) avec des acides sulfoniques à chaîne alkyle de grandes dimensions, et ayant la formule générale suivante:



(I)

dans laquelle R est un radical alkyle linéaire ou ramifié en C_6 à C_{18}, caractérisé en ce qu'on dissout le sel de sodium de l'acide sulfonique choisi dans de l'eau distillée, en ce qu'on dissout la MTA dans de l'eau distillée à laquelle on a ajouté du H_2SO_4 concentré, en ce qu'on fait réagir l'une avec l'autre les deux solutions pour récipiter le sulfonate de MTA et en ce qu'on récupère ce dernier sel à un degré élevé de pureté.

3. Procédé selon la revendication 2, caractérisé en ce que le sel de sodium de l'acide sulfonique subit cette dissolution à une température comprise entre 35 et 60°C, en ce qu'on utilise les quantités suivantes d'eau distillée par mole de sel: 3 litres pour l'hexanesulfonate, 10 litres pour l'octanesulfonate, 15 litres pour le décanesulfonate, 20 litres pour le dodécanesulfonate, 30 litres pour le tétradécanesulfonate, 40 litres pour l'hexadécanesulfonate et 50 litres pour l'octadécanesulfonate.

4. Procédé selon la revendication 2, caractérisé en ce que le MTA subit cette dissolution à une température comprise entre 40 et 60°C dans un mélange d'eau distillée et de H_2SO_4 contenant 3 litres d'eau distillée et 0,5 mole de H_2SO_4 par mole de MTA.

5. Procédé selon la revendication 2, caractérisé en ce que cette réaction est effectuée en ajoutant la solution de MTA refroidie à 15—25°C à la solution de sel de sodium de l'acide sulfonique, à une température comprise entre 35 et 60°C, en agitant, les deux réactifs étant dans des quantités équimolaires, le mélange étant maintenu sous agitation et refroidi à une température de 15 à 25°C pendant un temps compris entre 0,5 et 20 heures.

6. Procédé selon la revendication 2, caractérisé en ce que le sulfonate de MTA est récupéré par filtration sous pression ou par centrifugation puis lavage à l'eau distillée et séchage sous vide à une température de 40°C.

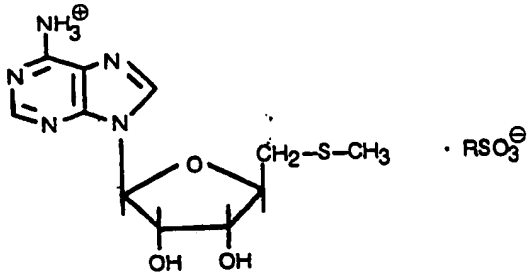
7. Compositions pharmaceutiques ayant une activité vasodilatatrice centrale et périphérique, anti-

agrégation plaquettaire, anti-inflammatoire, analgésique et antipyrétique, comprenant au moins un composé répondant à la formule générale (I) comme principe actif.

8. Utilisation d'un composé répondant à la formule générale (I) pour réparer des produits pharmaceutiques ayant une activité vasodilatatrice centrale et périphérique, anti-agrégation plaquettaire, anti-inflammatoire, analgésique et antipyrétique.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation de sels de la 5'-méthylthio-5'-désoxyadénosine (MTA) avec des acides sulfoniques à chaîne alkyle de grande longueur, et ayant la formule générale suivante:



(I)

dans laquelle R est un radical alkyle linéaire ou ramifié en C_6 à C_{18}, caractérisé en ce qu'on dissout le sel de sodium de l'acide sulfonique choisi dans de l'eau distillée, en ce qu'on dissout la MTA dans de l'eau distillée à laquelle on a ajouté du H_2SO_4 concentré, en ce qu'on fait réagir l'une avec l'autre les deux solutions pour récipiter le sulfonate de MTA et en ce qu'on récupère ce dernier sel à un degré élevé de pureté.

2. Procédé selon la revendication 1, caractérisé en ce que le sel de sodium de l'acide sulfonique subit cette dissolution à une température comprise entre 35 et 60°C, en ce qu'on utilise les quantités d'eau suivantes par mole de sel: 3 litres pour l'hexanesulfonate, 10 litres pour l'octanesulfonate, 15 litres pour le décanesulfonate, 20 litres pour le dodécanesulfonate, 30 litres pour le tétradécanesulfonate, 40 litres pour l'hexadécanesulfonate et 50 litres pour l'octadécanesulfonate.

3. Procédé selon la revendication 1, caractérisé en ce que le MTA subit cette dissolution à une température comprise entre 40 et 60°C dans un mélange d'eau distillée et de H_2SO_4 contenant 3 litres d'eau distillée et 0,5 mole de H_2SO_4 par mole de MTA.

4. Procédé selon la revendication 1, caractérisé en ce que cette réaction est effectuée en ajoutant la solution de MTA refroidie à 15—25°C à la solution de sel de sodium de l'acide sulfonique, à une température comprise entre 35 et 60°C, en agitant, les deux réactifs étant dans des quantités équimolaires, le mélange étant maintenu sous agitation et refroidi à une température de 15 à 25°C pendant un temps compris entre 0,5 et 20 heures.

5. Procédé selon la revendication 1, caractérisé en ce que le sulfonate de MTA submit cette récupération par filtration sous pression ou par centrifugation suivie d'un lavage à l'eau distillée et d'un séchage sous vide à une température de 40°C.